

BEST AVAILABLE COPY



PG1/EP200 4 / 0 0 6 4 2 7

14 06 2004

INVESTOR IN PEOPLE

EP-4/6427

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

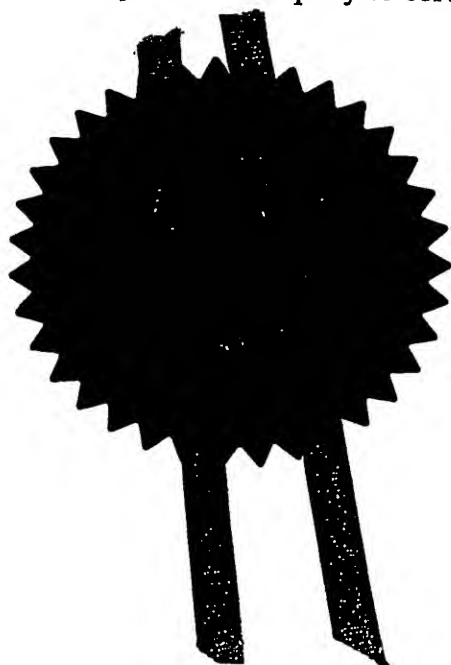
REC'D 07 JUL 2004	
WIPO	PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

Dated

P. Mahoney
13 May 2004



The
Patent
Office

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

17JUN03 E815407-1 D02029

P01/7700 0.00-1313915.1

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

JNR/HG/PB60273P

2. Patent application number

(The Patent Office will fill in his part)

0313915.1

16 JUN 2003

3. Full name, address and postcode of the or of each applicant (underline all surnames)

SmithKline Beecham Corporation
One Franklin Plaza, P.O. Box 7929, Philadelphia,
Pennsylvania 19101, United States of America

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

United States of America

5949417004

4. Title of the invention

Compounds

5. Name of your agent (if you have one)

Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number (if you know it)

8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (if you know it) the or each application number

Country	Priority application number (if you know it)	Date of filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer yes if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is named as an applicant, or
 - c) any named applicant is a corporate body
- See note (d)

Patents Form 1/77

9. Indicate the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form
Description
Claim(s)
Abstract
Drawings

35
2
1



10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11.

We request the grant of a patent on the basis of this application

Signature

J N Rice

Date 16-Jun-03

12. Name and daytime telephone number of person to contact in the United Kingdom

J N Rice 01279 644508

Warning

After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
- b) Write your answers in capital letters using black ink or you may type them.
- c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
- f) For details of the fee and ways to pay please contact the Patent Office.

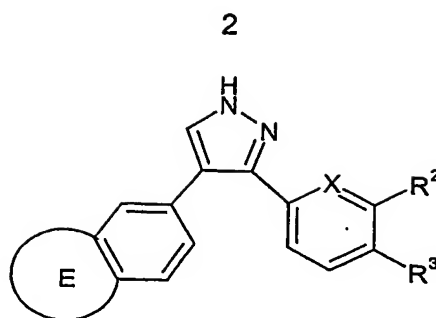
Compounds

This invention relates to novel pyrazole derivatives which are inhibitors of the transforming growth factor, ("TGF")- β signalling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF- β type I or activin-like kinase ("ALK")-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a disease state mediated by this pathway.

TGF- β 1 is the prototypic member of a family of cytokines including the TGF- β s, activins, inhibins, bone morphogenetic proteins and Müllerian-inhibiting substance, that signal through a family of single transmembrane serine/threonine kinase receptors. These receptors can be divided into two classes, the type I or activin like kinase (ALK) receptors and type II receptors. The ALK receptors are distinguished from the type II receptors in that the ALK receptors (a) lack the serine/threonine rich intracellular tail, (b) possess serine/threonine kinase domains that are very homologous between type I receptors, and (c) share a common sequence motif called the GS domain, consisting of a region rich in glycine and serine residues. The GS domain is at the amino terminal end of the intracellular kinase domain and is critical for activation by the type II receptor. Several studies have shown that TGF- β signaling requires both the ALK and type II receptors. Specifically, the type II receptor phosphorylates the GS domain of the type I receptor for TGF- β , ALK5, in the presence of TGF- β . The ALK5, in turn, phosphorylates the cytoplasmic proteins smad2 and smad3 at two carboxy terminal serines. The phosphorylated smad proteins translocate into the nucleus and activate genes that contribute to the production of extracellular matrix. Therefore, preferred compounds of this invention are selective in that they inhibit the type I receptor and thus matrix production.

Surprisingly, it has now been discovered that a class of novel pyrazoles derivatives function as potent and selective non-peptide inhibitors of ALK5 kinase.

According to a first aspect, the invention provides the use of a compound of formula (I), a pharmaceutically acceptable salt, solvate or derivative thereof;



(I)

wherein

ring E is a saturated, unsaturated or aromatic 5 or 6-membered heterocycle which heterocycle in addition to carbon contains one or more ring-heteroatoms independently selected from nitrogen and oxygen, wherein the heterocycle is optionally substituted on any nitrogen atom where appropriate by one or more groups R^{Ea} independently selected from C_{1-6} alkyl and C_{1-6} alkoxy C_{1-6} alkyl and is optionally substituted on any carbon atom where appropriate by one or more groups R^{Eb} independently selected from oxo, C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkyl, C_{1-6} alkoxy and halo;

X is N or CH;

R^2 is hydrogen, C_{1-6} alkyl, halo, cyano or perfluoro C_{1-6} alkyl; and

R^3 is hydrogen or halo;

in the preparation of a medicament for treating or preventing a disease or condition mediated by ALK-5 inhibition.

Preferably the benzofused ring system including E is selected from the list: benzimidazol-6-yl, benzimidazol-5-yl, benzoxazol-6-yl, benzoxazol-5-yl, 4H-benzo[1,4]oxazin-3-one-6-yl, benzo[1,3]dioxol-5-yl, benzodioxan-6-yl, quinolin-6-yl and benzotriazol-6-yl.

Preferably X is N.

Preferably R^2 is hydrogen, C_{1-6} alkyl, chloro or fluoro. More preferably R^2 is hydrogen, methyl, chloro or fluoro. More preferably still, R^2 is methyl.

Preferably R^3 is hydrogen or fluoro.

Preferably, when X is N, R^2 is methyl. More preferably when X is N and R^2 is methyl, R^3 is H.

It will be appreciated that the present invention is intended to include compounds having any combination of the preferred groups listed hereinbefore.

- 5 The term "ALK5 inhibitor" is used herein to mean a compound, other than inhibitory smads, e.g. smad6 and smad7, which selectively inhibits the ALK5 receptor preferentially over p38 or type II receptors.

- 10 Activation of the TGF- β 1 axis and expansion of extracellular matrix are early and persistent contributors to the development and progression of chronic renal disease and vascular disease. Border W.A., et al, N. Engl. J. Med., 1994; 331(19), 1286-92. Further, TGF- β 1 plays a role in the formation of fibronectin and plasminogen activator inhibitor-1, components of sclerotic deposits, through the action of smad3 phosphorylation by the TGF- β 1 receptor ALK5. Zhang Y., et al, Nature, 1998; 394(6696), 909-13; Usui T., et al, Invest. Ophthalmol. Vis. Sci., 1998; 39(11), 1981-9.

- Progressive fibrosis in the kidney and cardiovascular system is a major cause of suffering and death and an important contributor to the cost of health care. TGF- β 1 has been implicated in many renal fibrotic disorders. Border W.A., et al, N. Engl. J. Med., 1994; 331(19), 1286-92. TGF- β 1 is elevated in acute and chronic glomerulonephritis Yoshioka K., et al, Lab. Invest., 1993; 68(2), 154-63, diabetic nephropathy Yamamoto, T., et al, 1993, PNAS 90, 1814-1818., allograft rejection, HIV nephropathy and angiotensin-induced nephropathy Border W.A., et al, N. Engl. J. Med., 1994; 331(19), 1286-92. In these diseases the levels of TGF- β 1 expression coincide with the production of extracellular matrix. Three lines of evidence suggest a causal relationship between TGF- β 1 and the production of matrix. First, normal glomeruli, mesangial cells and non-renal cells can be induced to produce extracellular-matrix protein and inhibit protease activity by exogenous TGF- β 1 in vitro. Second, neutralising anti-bodies against TGF- β 1 can prevent the accumulation of extracellular matrix in nephritic rats. Third, TGF- β 1 transgenic mice or in vivo transfection of the TGF- β 1 gene into normal rat kidneys resulted in the rapid development of glomerulosclerosis. Kopp J.B., et al, Lab. Invest., 1996; 74(6), 991-1003. Thus, inhibition of TGF- β 1 activity is indicated as a therapeutic intervention in chronic renal disease.

- TGF- β 1 and its receptors are increased in injured blood vessels and are indicated in neointima formation following balloon angioplasty Saltis J., et al, Clin. Exp. Pharmacol. Physiol., 1996; 23(3), 193-200. In addition TGF- β 1 is a potent stimulator of smooth muscle cell ("SMC") migration in vitro and migration of SMC in the arterial wall is a contributing factor in the pathogenesis of atherosclerosis and restenosis.
- 5 Moreover, in multivariate analysis of the endothelial cell products against total cholesterol, TGF- β receptor ALK5 correlated with total cholesterol ($P < 0.001$) Blann A.D., et al, Atherosclerosis, 1996; 120(1-2), 221-6. Furthermore, SMC derived from human atherosclerotic lesions have an increased ALK5/TGF- β type II receptor ratio.
- 10 Because TGF- β 1 is over-expressed in fibroproliferative vascular lesions, receptor-variant cells would be allowed to grow in a slow, but uncontrolled fashion, while overproducing extracellular matrix components McCaffrey T.A., et al, Jr., J. Clin. Invest., 1995; 96(6), 2667-75. TGF- β 1 was immunolocalized to non-foamy macrophages in atherosclerotic lesions where active matrix synthesis occurs,
- 15 suggesting that non-foamy macrophages may participate in modulating matrix gene expression in atherosclerotic remodeling via a TGF- β -dependent mechanism. Therefore, inhibiting the action of TGF- β 1 on ALK5 is also indicated in atherosclerosis and restenosis.
- 20 TGF- β is also indicated in wound repair. Neutralising antibodies to TGF- β 1 have been used in a number of models to illustrate that inhibition of TGF- β 1 signalling is beneficial in restoring function after injury by limiting excessive scar formation during the healing process. For example, neutralising antibodies to TGF- β 1 and TGF- β 2 reduced scar formation and improved the cytoarchitecture of the neodermis by
- 25 reducing the number of monocytes and macrophages as well as decreasing dermal fibronectin and collagen deposition in rats Shah M., J. Cell. Sci., 1995, 108, 985-1002. Moreover, TGF- β antibodies also improve healing of corneal wounds in rabbits Moller-Pedersen T., Curr. Eye Res., 1998, 17, 736-747, and accelerate wound healing of gastric ulcers in the rat, Ernst H., Gut, 1996, 39, 172-175. These
- 30 data strongly suggest that limiting the activity of TGF- β would be beneficial in many tissues and suggest that any disease with chronic elevation of TGF- β would benefit by inhibiting smad2 and smad3 signaling pathways.
- 35 TGF- β is also implicated in peritoneal adhesions Saed G.M., et al, Wound Repair Regeneration, 1999 Nov-Dec, 7(6), 504-510. Therefore, inhibitors of ALK5 would be

beneficial in preventing peritoneal and sub-dermal fibrotic adhesions following surgical procedures.

- Therefore a disease or condition mediated by ALK-5 inhibition is preferably selected from the list: chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers (including diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers), ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis and primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis and keloids. Preferably kidney fibrosis.
15. Many of the compounds of formula (I) are novel. Therefore according to a second aspect the invention provides a compound as defined in the first aspect with the proviso that compound of formula (I) is not:
- 1,3-diethyl-1,3-dihydro-5-[3-(3-methylphenyl)-1H-pyrazol-4-yl]-2H-benzimidazol-2-one;
- 20 1,3-dihydro-1,3-dimethyl-5-(3-phenyl-1H-pyrazol-4-yl)-2H-benzimidazol-2-one, 1,3-diethyl-1,3-dihydro-5-(3-phenyl-1H-pyrazol-4-yl)-2H-benzimidazol-2-one; 1-ethyl-1,3-dihydro-3-methyl-5-[3-(3-methylphenyl)-1H-pyrazol-4-yl]-2H-benzimidazol-2-one;
- 1,3-diethyl-5-[3-(4-fluoro-3-methylphenyl)-1H-pyrazol-4-yl]-1,3-dihydro-2H-benzimidazol-2-one;
- 25 1,3-diethyl-5-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1,3-dihydro-2H-benzimidazol-2-one;
- 1,3-diethyl-1,3-dihydro-5-[3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl]-2H-benzimidazol-2-one;
- 30 1-ethyl-6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1H-benzimidazole;
- 1-ethyl-5-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1H-benzimidazole;
- 6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1-(1-methylethyl)-1H-benzimidazole;
- 5-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1-(1-methylethyl)-1H-benzimidazole;
- 6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1-(2-propoxyethyl)-1H-benzimidazole;
- 35 6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1-(1-propoxyethyl)-1H-benzimidazole;
- 6-[3-(4-bromophenyl)-1H-pyrazol-4-yl]-1-methyl-1H-benzimidazole;

6-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-1-methyl-1H-benzimidazole;
1-methyl-6-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-1H-benzimidazole;
6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1-methyl-1H-benzimidazole; or
5-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1-methyl-1H-benzimidazole;

5

According to a third aspect, the invention provides a compound as defined in the first aspect with the provisos that a) when the benzofused ring system including E is 1,3-dihydro-2H-benzimidazol-2-one-5-yl, X is not CH; b) when the benzofused ring system including E is benzimidazol-5-yl or benzimidazol-6-yl and X is CH, R³ is not halogen, and c) when the benzofused ring system including E is benzimidazol-6-yl and X is N, R² is not hydrogen.

10

According to a fourth aspect, the invention provides a compound as defined in the first aspect with the proviso that a) when the benzofused ring system including E is 1,3-dihydro-2H-benzimidazol-2-one-5-yl, X is not CH; and b) when the benzofused ring system including E is benzimidazol-5-yl or benzimidazol-6-yl, R² is not hydrogen.

15

Compounds of formula (I) which are of special interest as agents useful in the treatment or prophylaxis of disorders characterised by the overexpression of TGF- β are selected from the list:

20

4-[1-ethyl-benzimidazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole (Example 1);

4-[1-(2-methoxyethyl)-benzimidazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole (Example 2);

4-[1-(methyl)-benzimidazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole (Example 3);

25

4-[2-(methyl)-benzoxazol-6-yl]-3-[pyridin-2-yl]-1H-pyrazole (Example 4);

4-[2-(methyl)-benzoxazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole (Example 5);

4-[benzoxazol-6-yl]-3-[pyridin-2-yl]-1H-pyrazole (Example 6);

4-[benzoxazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole (Example 7);

4-[benzoxazol-5-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole (Example 8);

30

4-[2-methyl-benzoxazol-5-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole (Example 9);

4-[4-methyl-4H-benzo[1,4]oxazin-3-one-6-yl]-3-(6-methylpyridin-2-yl)-1H-pyrazole (Example 10);

4-[4-ethyl-4H-benzo[1,4]oxazin-3-one-6-yl]-3-(6-methylpyridin-2-yl)-1H-pyrazole (Example 11); and

35

and pharmaceutically acceptable salts, solvates and derivatives thereof.

5 The term "C₁₋₆alkyl" as used herein, whether on its own or as part of a group, refers to a straight or branched chain saturated aliphatic hydrocarbon radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl and hexyl.

10 The term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term "perfluoroalkyl" as used herein includes compounds such as trifluoromethyl.

15 The terms "halo" or "halogen" are used interchangeably herein to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

20 For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

25 For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

30 As used herein the term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, of the compound of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) the a compound of formula (I) or an active metabolite or residue thereof, eg, a prodrug. Preferred pharmaceutically acceptable derivatives according to the invention are any pharmaceutically acceptable salts, solvates or prodrugs.

35 Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and

tetraalkylammonium and the like, or mono- or di- basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like. Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Hereinafter, compounds, their pharmaceutically acceptable salts, their solvates and polymorphs, defined in any aspect of the invention (except intermediate compounds in chemical processes) are referred to as "compounds of the invention".

Compounds of the invention may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The compounds of the invention may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention.

Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.

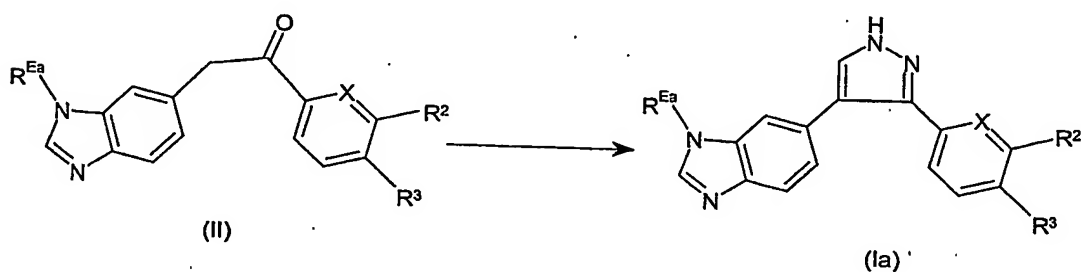
Compounds of the invention may be prepared, in known manner in a variety of ways. In the following reaction schemes and hereafter, unless otherwise stated R^1 to R^3 , X

and E are as defined in the first aspect. These processes form further aspects of the invention.

Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc. Subsets of these general formulae are defined as (Ia), (Ib), (Ic) etc (IVa), (IVb), (IVc) etc.

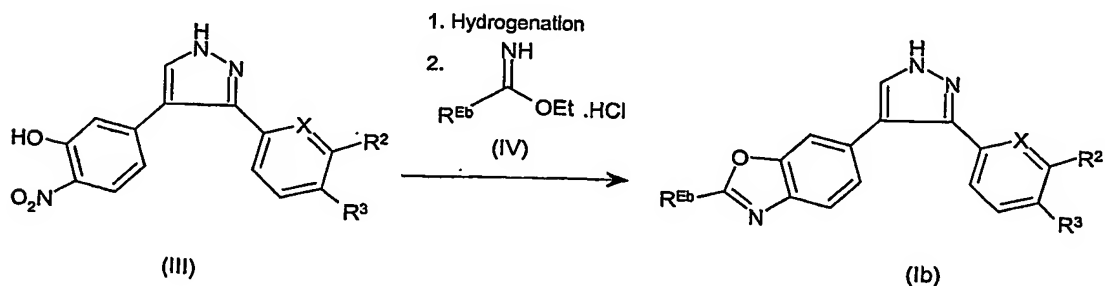
Compounds of formula (Ia), i.e. compounds of general formula (I) where the benzofused ring system including E is benzimidazol-6-yl, may be prepared from compounds of formula (II) according to reaction scheme 1 by treating (II) with N,N-dimethylformamide dimethyl acetal in THF and acetic acid at room temperature followed by addition of hydrazine at room temperature.

Scheme 1



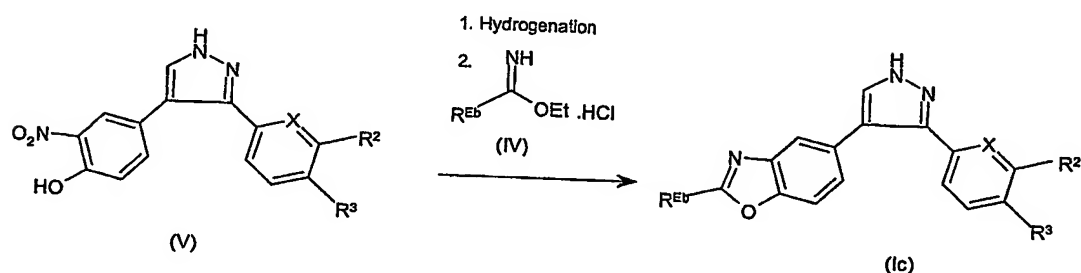
Compounds of formula (Ib), i.e. compounds of general formula (I) where the benzofused ring system including E is benzoxazol-6-yl, may be prepared from compounds of formula (III) according to reaction scheme 2 by treating (III) with hydrogen in presence of Pd/C in a suitable solvent such as ethanol or tetrahydrofuran at room temperature followed by treatment with a compound of formula (IV) in a suitable solvent such as ethanol at elevated temperature.

Scheme 2

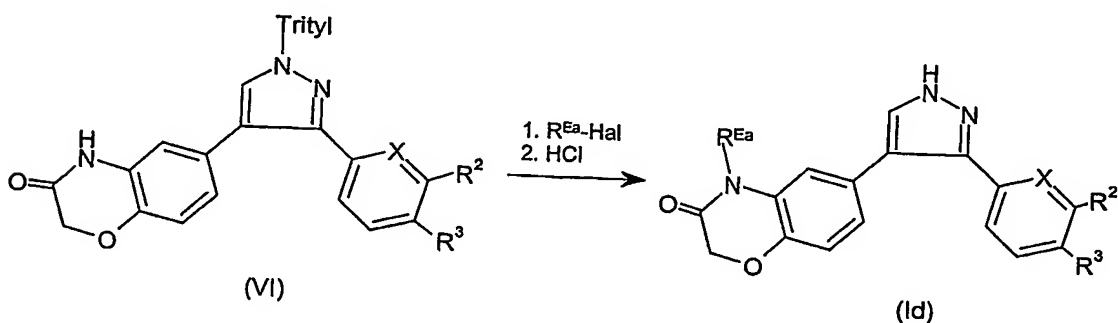


Compounds of formula (Ic), i.e. compounds of general formula (I) where the benzofused ring system including E is benzoxazol-5-yl, may be prepared from compounds of formula (V) according to reaction scheme 3 by treating (V) with hydrogen in presence of Pd/C in a solvent such as ethanol or tetrahydrofuran at room temperature followed by treatment with a compound of formula (IV) in a suitable solvent such as ethanol at elevated temperature.

Scheme 3



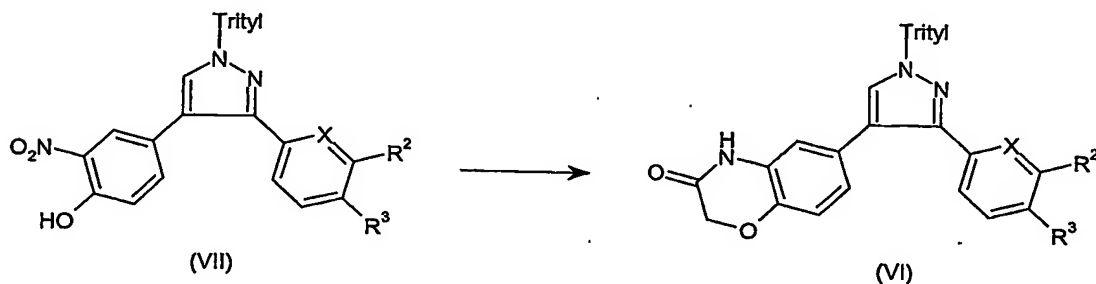
Compounds of formula (Id), i.e. compounds of general formula (I) where the benzofused ring system including E is 4H-benzo[1,4]oxazin-3-one-6-yl, may be prepared from compounds of formula (VI) according to reaction scheme 4 by treating (VI) with $\text{R}^{\text{Ea}}\text{-Hal}$ (where Hal is halogen) in a solvent such as acetone in the presence of a base such as caesium carbonate at elevated temperature, followed by treatment with hydrochloric acid in a solvent such as an alcohol at reflux.



Compounds of formula (VI) may be prepared from compounds of formula (VII) according to reaction scheme 5 by treating (VII) with ethyl bromoacetate in a solvent

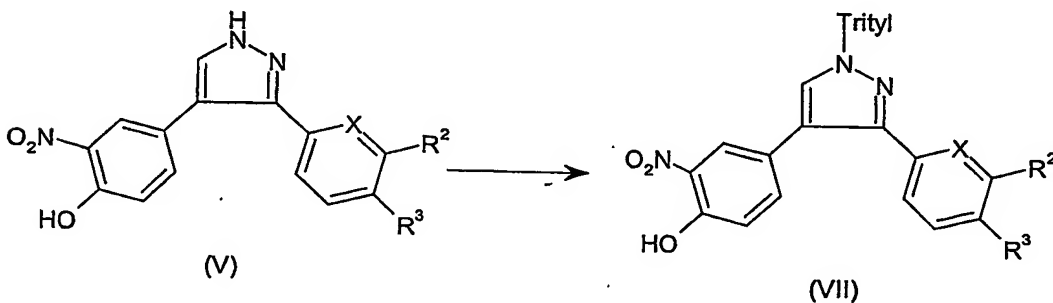
such as acetone in the presence of a base such as caesium carbonate at room temperature followed by treatment with iron in acetic acid at elevated temperature.

Scheme 5

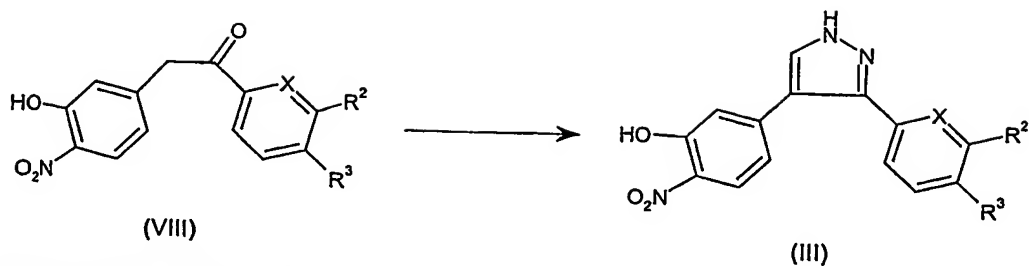


Compounds of formula (VII) may be prepared from compounds of formula (V) according to reaction scheme 6 by treating (V) with trityl chloride in a solvent such as methylene chloride in the presence of a base such as triethylamine at room temperature.

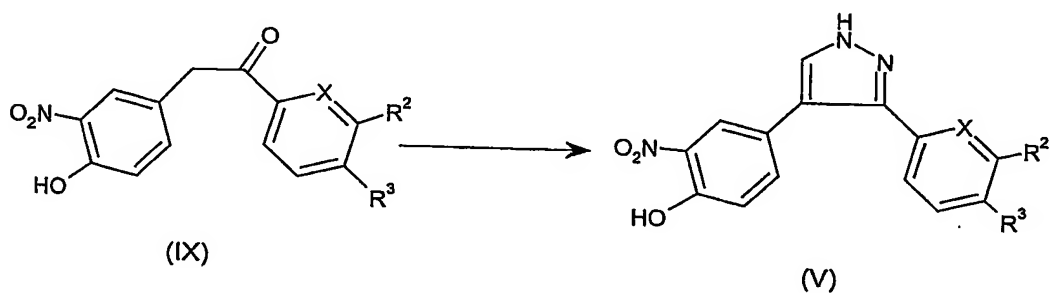
Scheme 6



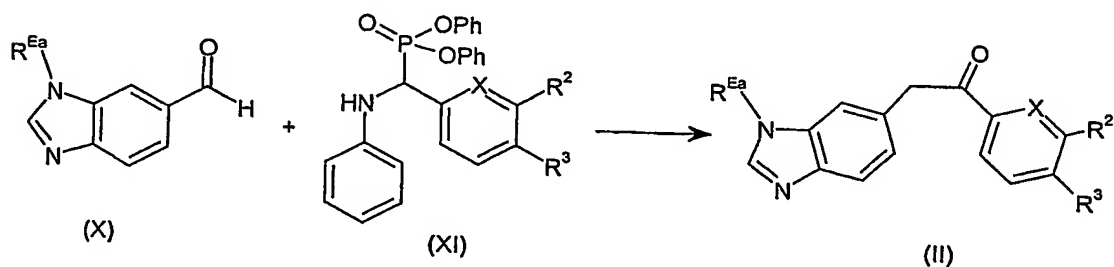
15 Compounds of formula (III) (see scheme 2) may be prepared from compounds of formula (VIII) according to reaction scheme 7 using analogous methods described for reaction scheme 1.

Scheme 7

Compounds of formula (V) (see scheme 3) may be prepared from compounds of formula (IX) according to reaction scheme 8 using analogous methods described for reaction scheme 1.

Scheme 8

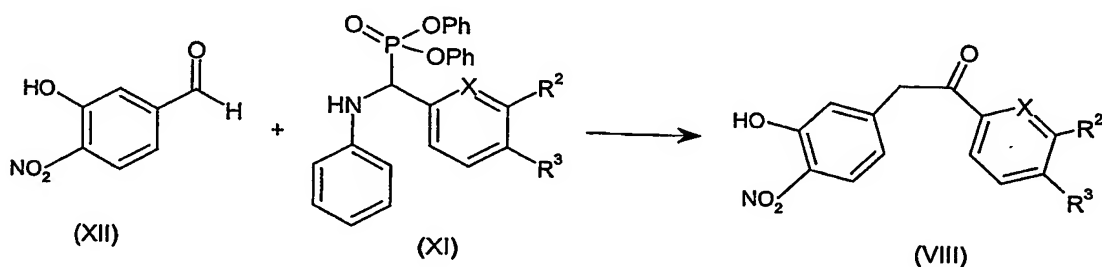
- 10 Compounds of formula (II) (see scheme 1) may be prepared according to reaction scheme 9 by reacting aldehydes of formula (X) with N,P acetals of formula (XI) followed by hydrolysis of the resulting enamine (see M. Journet, *Tetrahedron Letters*, 1998, 39, 1717-1720 and I. W. Davies *et al.*, *J. Org. Chem.*, 2000, 65, 8415-8420). Preferred reaction conditions comprise treatment with a suitable base, such as
- 15 caesium carbonate or potassium tert-butoxide, in a suitable solvent such as tetrahydrofuran and isopropyl alcohol. The enamine may be hydrolysed with hydrochloric acid.

Scheme 9

Compounds of formula (VIII) (see scheme 7) may be prepared from aldehydes of formula (XII) and N,P acetals of formula (XI) according to reaction scheme 10 using the same conditions as described for reaction Scheme 9.

5

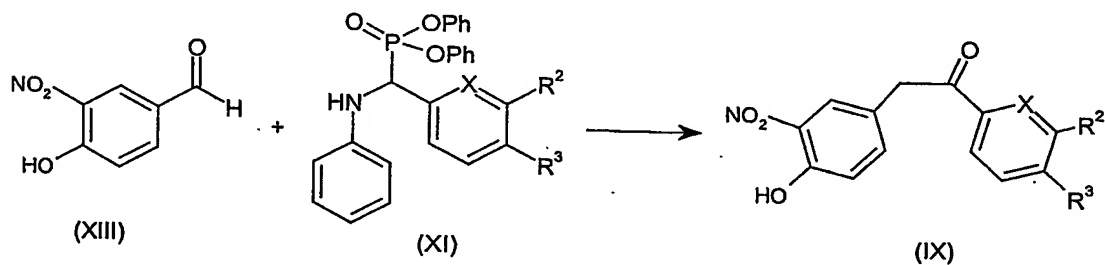
Scheme 10



Compounds of formula (IX) (see scheme 8) may be prepared from 4-hydroxy-3-nitrobenzaldehyde (XIII) and N,P acetals of formula (XI) according to reaction scheme 11 using analogous methodology to that described for reaction Scheme 10.

10

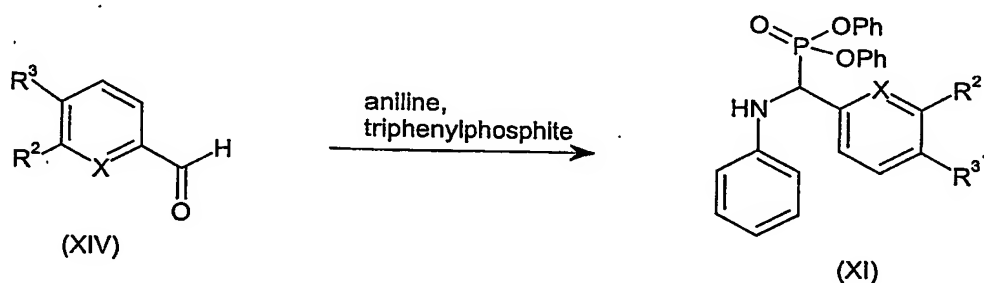
Scheme 11



Compounds of formula (XI) may be prepared from compounds of formula (XIV) according to reaction scheme 12 by treating compounds of formula (XIV) with aniline and diphenylphosphite in a suitable solvent such as isopropanol.

15

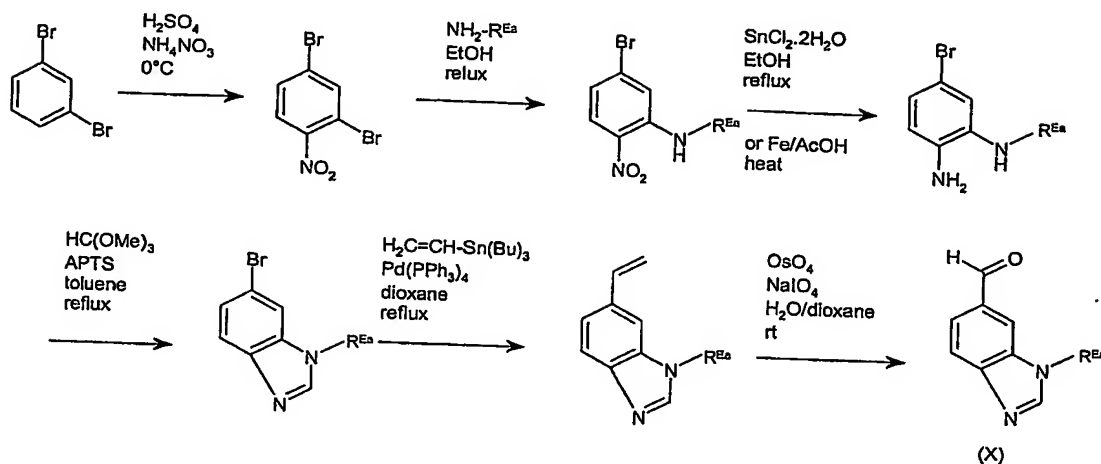
Scheme 12



20

Compounds of formula (X) (see scheme 9) may be prepared following the general methodology described in Scheme 13.

Scheme 13



Further details for the preparation of compounds of formula (I) are found in the examples.

10 The compounds of the invention may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds. Libraries of compounds of the invention may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either

15 solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect there is provided a compound library comprising at least 2 compounds of the invention.

20 It will be appreciated that references herein to treatment extend to prophylaxis as well as the treatment of established conditions. It will further be appreciated that references herein to treatment or prophylaxis of disorders characterised by the overexpression of TGF- β , shall include the treatment or prophylaxis of TGF- β associated disease such as fibrosis, especially liver and kidney fibrosis, cancer development, abnormal bone function and inflammatory disorders, and scarring.

25

Other pathological conditions which may be treated in accordance with the invention have been discussed in the introduction hereinbefore. The compounds of the

present invention are particularly suited to the treatment of fibrosis and related conditions.

5 Compounds of the present invention may be administered in combination with other therapeutic agents, for example antiviral agents for liver diseases, or in combination with ACE inhibitors or angiotensin II receptor antagonists for kidney diseases.

10 The compounds of the invention may be administered in conventional dosage forms prepared by combining a compound of the invention with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

15 The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

20 The compositions may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

25 The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

30 The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

35 Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example

lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

No toxicological effects are indicated when a compound of the invention is administered in the above-mentioned dosage range.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

It will be appreciated that the invention includes the following further aspects. The preferred embodiments described for the first aspect extend these further aspects:

- i) a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or diluent;
- ii) a compound of the invention for use as a medicament;

- iii) a method of treatment or prophylaxis of a disorder selected from chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers (including diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers), ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis and primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis and keloids, in mammals, which comprises administration to the mammal in need of such treatment, an effective amount of a compound of the invention; and
- iv) a combination of a compound of the invention with an ACE inhibitor or an angiotensin II receptor antagonist.

The following non-limiting examples illustrate the present invention.

Abbreviations

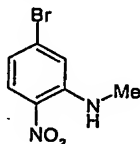
20	APTS	-	p-toluene sulfonic acid
	Binap	-	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	CH ₂ Cl ₂	-	dichloromethane
	CDCl ₃	-	deuterium chloroform
	CH ₃ CN	-	acetonitrile
25	DMF.DMA	-	dimethylformamide dimethylacetal
	EtOH	-	ethanol
	EtOAc	-	ethyl acetate
	IPrOH	-	isopropanol
	MeOH	-	methanol
30	NaOH	-	sodium hydroxide
	NaHCO ₃	-	sodium bicarbonate
	Na ₂ SO ₄	-	sodium sulfate
	THF	-	tetrahydrofuran
	TEA	-	triethylamine
35	DME	-	dimethoxyethane
	Pd/C	-	palladium on activated carbon

$\text{Pd}_2(\text{dba})_3$ - bis (dibenzylidene acetone)palladium
 $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ - tin(II) chloride dihydrate

Intermediate 1: 2,4-dibromo-nitrobenzene

- 5 To an iced cold solution of 1,3-dibromobenzene (10g, 42.3mmol) in sulfuric acid (200ml) was added portionwise ammonium nitrate (3.39g, 42.3mmol) and the mixture was stirred at 0°C for 10 minutes and then poured into water. After extraction with CH_2Cl_2 , the organic phase was washed with a saturated solution of NaHCO_3 , dried over Na_2SO_4 and concentrated under reduced pressure. After trituration with
- 10 pentane, the title compound was obtained as a pale yellow solid (8g, 67.2%); NMR H^1 (300MHz, CDCl_3 , ppm) δ : 7.95 (s, 1H), 7.75 (d, 1H), 7.6 (d, 1H).

Intermediate 2: 4-bromo-2-(methylamino)-nitrobenzene



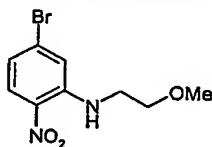
- 15 To a solution of intermediate 1 (8g, 28.5 mmol) in EtOH (200ml) was added a solution of methylamine 40% in water (200ml) and the mixture was heated under reflux for 2 hours and then cooled. The resulting precipitate was filtered and dried. The title compound was obtained as an orange solid (5g, 76%); m.p. 130-132°C.

20 Intermediate 3: 4-bromo-2-(ethylamino)-nitrobenzene



- Intermediate 1 (6g, 28mmol) and ethylamine (solution 70% in water, 200ml) were reacted as described for intermediate 2 to afford the title compound as a yellow solid (5g, 99.9%); NMR H^1 (300MHz, CDCl_3 , ppm) δ : 8.25 (s, 1H), 8.1 (d, 1H), 7.05 (s, 1H), 6.85 (d, 1H), 3.25 (m, 2H), 1.3 (t, 3H).
- 25

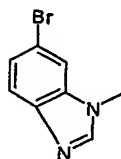
Intermediate 4: 4-bromo-2-(2-methoxyethylamino)-nitrobenzene



Intermediate 1 (6g, 28mmol) was reacted with 2-methoxyethylamine as described for intermediate 2, to afford the title compound as a solid (6g, 99.9%); NMR H^1 (300MHz, $CDCl_3$, ppm) δ : 8.3 (ls, 1H), 8.1 (d, 1H), 7.1 (s, 1H), 6.85 (d, 1H), 3.8 (m, 2H), 3.6 (m, 2H), 3.5 (s, 3H).

5

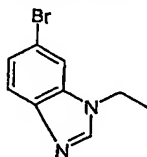
Intermediate 5: 1-methyl-6-bromo-benzimidazole



To a solution of intermediate 2 (5g, 21.6mmol) in EtOH (200ml) was added portionwise $SnCl_2 \cdot 2H_2O$ (9.8g, 43mmol) and the mixture was heated under reflux for 4 hours and then concentrated under reduced pressure. The residue was treated with water (200ml) and 1N NaOH (100ml). After extraction with CH_2Cl_2 , the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure.

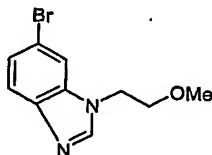
The residue was dissolved in toluene (50ml) and trimethylorthoformate (2.6ml, 24 mmol) and APTS (0.2g) were added and the mixture was heated under reflux for 2 hours and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with $CH_2Cl_2/MeOH$ (95/5). The title compound was obtained as a cream powder (2.5g, 54.74%); m.p. 126-128°C.

Intermediate 6: 1-ethyl-6-bromo-benzimidazole



Intermediate 3 (5g, 22 mmol) was reacted as described for intermediate 5, to afford the title compound as a brown oil (2.3g, 47.23%); NMR H^1 (300MHz, $CDCl_3$, ppm) δ : 8.00 (s, 1H), 7.75 (d, 1H), 7.65 (s, 1H), 7.45 (d, 1H), 4.25 (q, 2H), 1.6 (t, 3H).

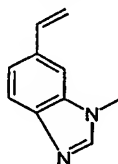
Intermediate 7: 1-(2-methoxyethyl)-6-bromo-benzimidazole



To a solution of intermediate 4 (6g, 22mmol) in acetic acid (100ml) at 60°C was added portionwise under vigorous stirring, iron (12g, 220mmol) and the mixture was

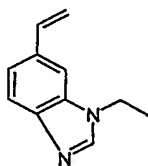
heated at 60°C for 2 hours and then cooled. The reaction mixture was basified by addition of a solution of sodium hydroxide, filtered on a celite pad and the filtrate was extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in toluene (80ml) and trimethylorthoformate (3.5ml, 32mmol) and APTS (0.6g) were added and the mixture was heated under reflux overnight and then concentrated under reduced pressure. The residue was purified by chromatography on silicagel eluting with CH₂Cl₂/MeOH (9/1). The title compound was obtained as an oil (6g, 96.07%); NMR H¹ (300MHz, CDCl₃, ppm) δ: 8.1 (s, 1H), 7.8 (d, 1H), 7.7 (s, 1H), 7.5 (d, 1H), 4.4 (t, 2H), 3.85 (t, 2H), 3.4 (s, 3H).

Intermediate 8: 1-methyl-6-vinyl-benzimidazole



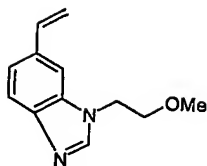
To a solution of intermediate 5 (2.5g, 11.8 mmol) in dioxane (100ml) were added tributyl(vinyl)tin (5.2ml, 18 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.69g, 0.5mmol) and the mixture was heated under reflux for 24 hours and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with CH₂Cl₂/MeOH (95/5). The title compound was obtained as an oil (1.8g, 96.1%); NMR H¹ (300MHz, CDCl₃, ppm) δ: 7.9 (s, 1H), 7.75 (d, 1H), 7.4 (m, 2H), 6.85 (dd, 1H), 5.8 (d, 1H), 5.25 (d, 1H), 3.85 (s, 3H).

Intermediate 9: 1-ethyl-6-vinyl-benzimidazole



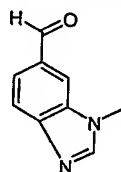
Intermediate 6 (2.3g, 10mmol) was reacted as described for intermediate 8 to afford the title compound as an oil (1.5g, 85.31%); NMR H¹ (300MHz, CDCl₃, ppm) δ: 7.9 (s, 1H), 7.75 (d, 1H), 7.4 (m, 2H), 6.95 (m, 1H), 5.8 (m, 1H), 5.25 (m, 1H), 4.2 (q, 2H), 1.55 (t, 3H).

Intermediate 10: 1-(2-methoxyethyl)-6-vinyl-benzimidazole



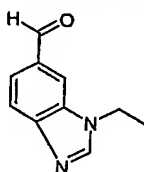
Intermediate 7 (6g, 23.5mmol) was reacted as described for intermediate 8 to afford the title compound as an oil (3.5g, 73.64%); NMR H^1 (300MHz, $CDCl_3$, ppm) δ : 7.95 (s, 1H), 7.75 (d, 1H), 7.4 (m, 2H), 6.9 (m, 1H), 5.85 (d, 1H), 5.25 (m, 1H), 4.35 (t, 2H), 3.75 (t, 2H), 3.3 (s, 3H).

Intermediate 11: 1-methyl-6-formyl-benzimidazole



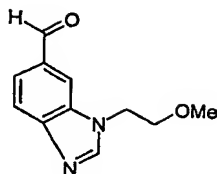
To a solution of intermediate 8 (1.8g, 11.4mmol) in dioxane (100ml) and water (14ml) was added osmium tetroxide (solution 2.5% in water, 6ml) and the mixture was stirred for 5 minutes at room temperature. Then sodium periodate (5.1g, 23.9mmol) was added and the mixture was stirred at room temperature for 3 hours and then poured into water. The aqueous phase was extracted with CH_2Cl_2 , the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The title compound was obtained as a cream powder (1g, 55%); m.p. 132-134°C.

Intermediate 12: 1-ethyl-6-formyl-benzimidazole



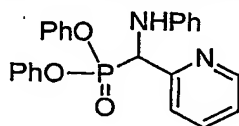
Intermediate 9 (1.5g, 8.8mmol) was reacted as described for intermediate 11 to afford the title compound as an oil (1.3g, 85.67%); NMR H^1 (300MHz, $CDCl_3$, ppm) δ : 10.1 (s, 1H), 8.15 (s, 1H), 8.05 (s, 1H), 7.95 (d, 1H), 7.85 d, 1H), 4.3 (q, 2H), 1.6 (t, 3H).

Intermediate 13: 1-(2-methoxyethyl)-6-formyl-benzimidazole



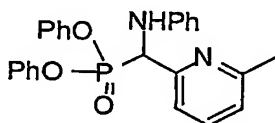
Intermediate 10 (3.5g, 17.33mmol) was reacted as described for intermediate 11 to afford the title compound as an oil (1.3g, 36.78%); NMR H^1 (300MHz, $CDCl_3$, ppm) δ : 10.05 (s, 1H), 8.15 (s, 1H), 8 (s, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 4.4 (t, 2H), 3.7 (t, 2H), 3.3 (s, 3H).

Intermediate 14: (phenylamino -pyridin-2-yl-methyl)-phosphonic acid diphenylester



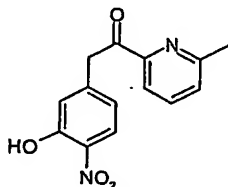
To a solution of 2-pyridinecarboxaldehyde (15g, 140mmol) in iPrOH (200ml) were added aniline (1.2eq, 15.65g, 168mmol) and diphenylphosphite (37.5ml, 197mmol). The reaction mixture crystallised after 30min at room temperature. isopropanol (300ml) was added and the mixture was allowed to stir for 2h. The resulting solid was filtered and dried to give the title compound as a white solid (56g, 96.15%); m.p. 130-132°C.

Intermediate 15: [(6-Methylpyridin-2-yl)-phenylamino-methyl]-phosphonic acid diphenylester



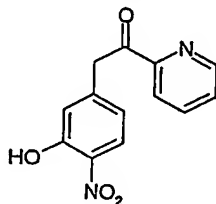
6-Methyl-2-pyridinecarboxaldehyde (10g, 83mmol) was reacted with aniline and diphenylphosphite as described for Intermediate 14, to afford the title compound as a white solid (40g, 99.53%); m.p. 110-112°C.

Intermediate 16: 2-[3-hydroxy-4-nitrophenyl]-1-[6-methylpyridin-2-yl]-ethanone



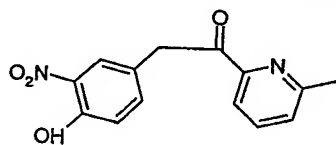
To a solution of 3-hydroxy-4-nitro-benzaldehyde (15g, 90mmol) and intermediate 15 (38.62g, 90mmol) in THF (200ml) and iPrOH (200ml) was added caesium carbonate (88g, 27mmol) and the mixture was stirred at room temperature overnight. The mixture was acidified to pH3 by addition of a solution of 4N HCl, and allowed to stir at room temperature for 2 hours and then poured into water. After neutralisation with a solution of 1N NaOH, the aqueous phase was extracted with CH₂Cl₂, the organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with CH₂Cl₂/MeOH (8/2). The title compound was obtained as an orange solid (15g, 61.4%); m.p. 128-130°C.

Intermediate 17: 2-[3-hydroxy-4-nitrophenyl]-1-[pyridin-2-yl]-ethanone



4-Nitro-3-(t-butyl-dimethylsilyloxy)-benzaldehyde (5g, 17.8mmol) and intermediate 14 (7.4g, 17.8mmol) were reacted as described for intermediate 16 to afford, after chromatography on silica gel (CH₂Cl₂/MeOH, 98/2), the title compound as a brown solid (3g, 64.85%); NMR H¹ (300MHz, CDCl₃, ppm) δ : 10.55 (s, 1H), 8.7 (d, 1H), 8.05 (m, 2H), 7.85 (t, 1H), 7.5 (m, 1H), 7.1 (s, 1H), 6.95 (d, 1H), 4.55 (s, 2H).

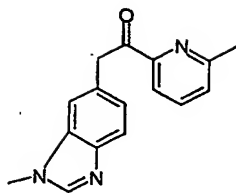
Intermediate 18: 2-[4-hydroxy-3-nitrophenyl]-1-[6-methylpyridin-2-yl]-ethanone



Intermediate 15 (14.2g, 33mmol) and 4-hydroxy-3-nitro-benzaldehyde (5g, 30 mmol) were reacted as described for intermediate 16 to afford, after chromatography on silica gel (CH₂Cl₂), the title compound as a brown oil (3.5g, 42.97%); NMR H¹ (300MHz, CDCl₃, ppm) δ : 10.25 (s, 1H), 8.7 (d, 1H), 8.2 (s, 1H), 7.7 (m, 1H), 7.15 (m, 1H), 6.9 (t, 1H), 6.8 (d, 1H), 4.5 (s, 2H), 2.65 (s, 3H).

Intermediate 19: 2-[1-methyl-benzimidazol-6-yl]-1-[6-methylpyridin-2-yl]-ethanone

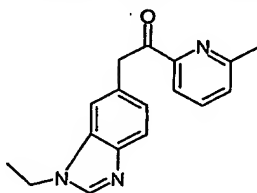
25



Intermediate 11 (3g, 18.8 mmol) and intermediate 15 (9.68g, 22.5mmol) were reacted as described for intermediate 16 to afford the title compound as a solid (1.1g, 22.14%); m.p. 96-98°C.

5

Intermediate 20: 2-[1-ethyl-benzimidazol-6-yl]-1-[6-methylpyridin-2-yl]-ethanone

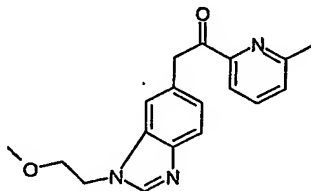


Intermediate 12 (1.3g, 7.5mmol) and intermediate 15 (3.86g, 9mmol) were reacted as described for intermediate 16 to afford the title compound as a brown oil (1g, 47.97%); NMR H^1 (300MHz, $CDCl_3$, ppm) δ : 7.9 (s, 1H), 8 (m, 1H), 7.85 (m, 1H), 7.55 (s, 1H), 7.35 (m, 1H), 7.2 (m, 1H), 6.9 (m, 1H), 4.7 (s, 2H), 4.25 (q, 2H), 2.65 (s, 3H), 1.55 (t, 3H).

10

Intermediate 21: 2-[1-(2-methoxyethyl)-benzimidazol-6-yl]-1-[6-methylpyridin-2-yl]-ethanone

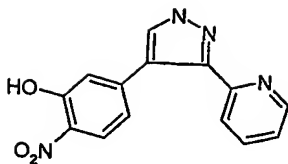
15



Intermediate 13 (1.3g, 6.4mmol) and intermediate 15 (3.29g, 7.6mmol) were reacted as described for intermediate 16 to afford the title compound as a brown oil (1.2g, 60.94%); NMR H^1 (300MHz, $CDCl_3$, ppm) δ : 8.00 (s, 1H), 7.9 (m, 1H), 7.75 (m, 2H), 7.45 (s, 1H), 7.3 (m, 1H), 7.1 (m, 1H), 4.7 (s, 2H), 4.3 (t, 2H), 3.7 (t, 2H), 3.3 (s, 3H), 2.6 (s, 3H).

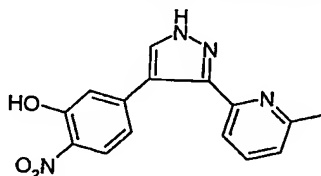
20

Intermediate 22: 4-[3-hydroxy-4nitro-phenyl]-3-[pyridin-2-yl]-1H-pyrazole



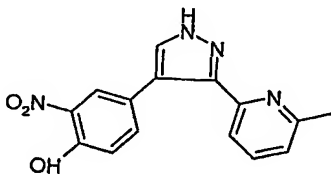
To a solution of intermediate 17 (2g, 7.7mmol) in THF (80ml) and acetic acid (1ml) was added DMF.DMA (1.5ml) and the mixture was stirred at room temperature for 5 hours. Then hydrazine hydrate (3ml) was added and the mixture was stirred at room temperature for 5 hours and then poured into water. The aqueous phase was extracted with CH₂Cl₂, the organic phase dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with CH₂Cl₂/MeOH (95/5). The title compound was obtained as a brown solid (1g, 46.1%); m.p. 170-172°C; [APCI MS] m/z 283 MH⁺.

Intermediate 23: 4-[3-hydroxy-4-nitro-phenyl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



Intermediate 16 (1g, 3.67mmol) was reacted as described for intermediate 22, to afford, after chromatography on silicagel (CH₂Cl₂/MeOH, 9/1), the title compound as a solid (1.1g, 99.9%); [APCI MS] m/z= 297 MH⁺.

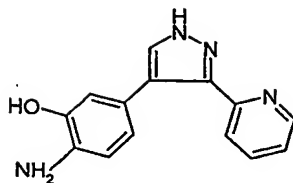
Intermediate 24: 4-[4-hydroxy-3-nitro-phenyl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



Intermediate 18 (3.5g, 12.87mmol) was reacted as described for intermediate 22, to afford, after chromatography on silica gel (CH₂Cl₂/MeOH, 9/1), the title compound as a yellow oil (1.2g, 31.5%); NMR H¹ (300MHz, CDCl₃, ppm) δ: 10.35 (s, 1H), 8.2 (m, 1H), 7.7 (m, 1H), 7.65 (s, 1H), 7.4 (m, 2H), 7.2 (m, 1H), 7.1 (m, 1H), 2.6 (s, 3H).

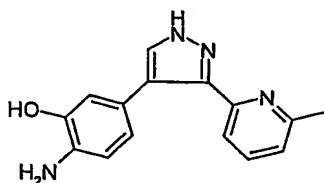
Intermediate 25: 4-[4-amino-3-hydroxy-phenyl]-3-[pyridin-2-yl]-1H-pyrazole

27



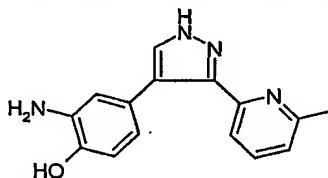
To a solution of intermediate 22 (1g, 3.5mmol) in EtOH (100ml) and THF (50ml) was added Pd/C 10% (100mg), and the mixture was hydrogenated at room temperature under 1.5 bars for 5 hours. The reaction mixture was purged with argon, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The title compound was obtained as a red solid (0.68g, 76.1%); [APCI MS] m/z : 253 MH^+ .

Intermediate 26: 4-[4-amino-3-hydroxy-phenyl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



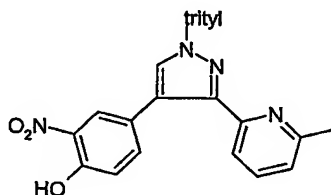
Intermediate 23 (1.1g, 3.7mmol) was reacted as described for intermediate 25 to afford, the title compound as an orange oil (0.9g, 91.04%); [APCI MS] m/z = 267 MH^+ .

Intermediate 27: 4-[3-amino-4-hydroxy-phenyl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



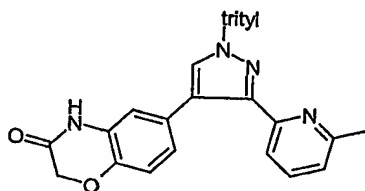
Intermediate 24 (1.2g, 4.05mmol) was reacted as described for intermediate 25 to afford, after chromatography on silica gel ($CH_2Cl_2/MeOH$, 9/1), the title compound as a yellow oil (0.5g, 46.36%); [APCI MS] m/z = 267 MH^+ .

Intermediate 28: 4-[4-hydroxy-3-nitro-phenyl]-3-[6-methylpyridin-2-yl]-1-trityl-1H-pyrazole



To a solution of intermediate 24 (4.47g, 16 mmol) in CH_2Cl_2 (100 ml) were added triethylamine (3.4 ml, 24 mmol) and trityl chloride (6.8g, 24 mmol) and the mixture was heated under reflux for 16 hours and then poured into water. After extraction with CH_2Cl_2 , the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The title compound was obtained as an oil (7.5g, 84.24%); NMR H^1 (300MHz, CDCl_3 , ppm) δ : 8.1 (s, 1H), 7.45 (m, 3H), 7.35 to 7.15 (m, 15H), 6.95 (d, 1H), 6.8 (d, 1H), 2.35 (s, 3H).

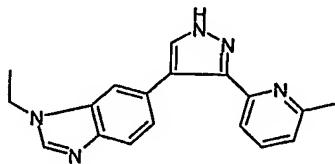
Intermediate 29 :4-[4H-benzo[1,4]oxazin-3-one-6-yl]-3-[6-methylpyridin-2-yl]-1-trityl-1H-pyrazole



To a solution of intermediate 28 (7.5g, 13.6 mmol) in acetone (200ml) were added caesium carbonate (7.3g, 24 mmol) and ethyl bromo acetate (4g, 24 mmol) and the mixture was stirred at room temperature for 2 hours and then poured into water. After extraction with CH_2Cl_2 , the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2). The resulting yellow oil (5g, 8 mmol) was dissolved in acetic acid (250 ml) and iron (4.5g, 80 mmol) was added portionwise. The mixture was heated at 60°C for 3 hours and then poured into water. The mixture was basified with aqueous NaOH and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 , filtered on a celite pad, and concentrated under reduced pressure. The title compound was obtained as a brown oil (3.2g, 42.98%); [APCI MS] m/z 549 MH^+ and 307 MH^+ (-trityl).

Examples

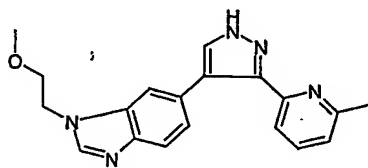
Example 1: 4-[1-ethyl-benzimidazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



To a solution of intermediate 20 (0.5g, 1.8mmol) in THF (80ml) and acetic acid (0.3ml) was added DMF.DMA (0.4ml) and the mixture was stirred at room

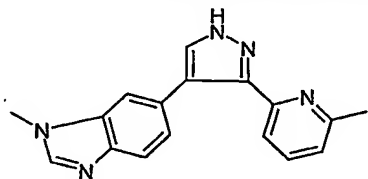
temperature for 4 hours. Then hydrazine hydrate (0.7ml) was added and the mixture was stirred at room temperature for 48 hours and then poured into water. The aqueous phase was extracted with CH_2Cl_2 , the organic phase dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9/1). After crystallisation from ethyl acetate, the title compound was obtained as cream crystals (0.17g, 31.31%); m.p. 182-184°C; [APCI MS] $m/z = 304 \text{ MH}^+$.

Example 2: 4-[1-(2-methoxyethyl)-benzimidazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



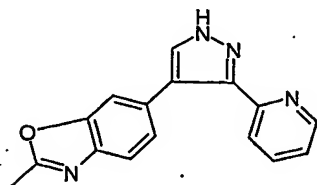
Intermediate 21 (0.6g, 1.9 mmol) was reacted as described for example 1 to afford, after crystallisation from ethanol, the title compound as crystals (0.3g, 47.41%); m.p. 172-174°C; [APCI MS] $m/z = 334 \text{ MH}^+$.

Example 3: 4-[1-(methyl)-benzimidazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



Intermediate 19 (0.5g, 1.9 mmol) was reacted as described for example 1 to afford, after trituration with pentane, the title compound a solid (0.21g, 38.51%); [APCI MS] $m/z = 290 \text{ MH}^+$.

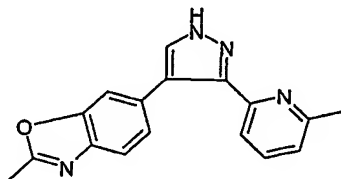
Example 4: 4-[2-(methyl)-benzoxazol-6-yl]-3-[pyridin-2-yl]-1H-pyrazole



To a solution of intermediate 25 (0.504g, 2mmol) in EtOH (20ml) was added ethyl acetimidate hydrochloride (0.247g, 2 mmol) and the mixture was heated under reflux for 4 hours and then concentrated. The residue was treated with water and extracted

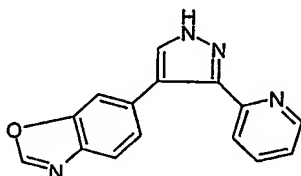
with CH_2Cl_2 . The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9/1). After trituration with pentane, the title compound was obtained as a cream solid (0.42g, 76.1%); m.p. 138-140°C; [APCI MS] $m/z = 277$ MH^+ .

Example 5: 4-[2-(methyl)-benzoxazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



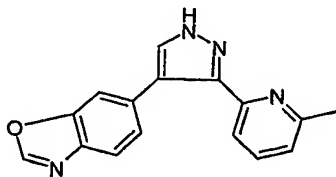
Intermediate 26 (0.45g, 1.69mmol) and ethyl acetimidate hydrochloride (0.315g, 2.5mmol) were reacted as described for example 4 to afford, after chromatography on silicagel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9/1), the title compound as a cream oil (0.3g, 61.15%); [APCI MS] $m/z = 291$ MH^+ .

Example 6: 4-[benzoxazol-6-yl]-3-[pyridin-2-yl]-1H-pyrazole



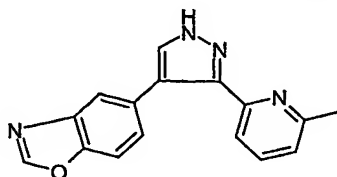
Intermediate 25 (0.504g, 2mmol) and ethyl formimidate hydrochloride (0.219g, 2mmol) were reacted as described for example 4 to afford, after trituration with pentane, the title compound as a cream solid (0.27g, 51.53%); m.p. 176-178°C; [APCI MS] $m/z = 263$ MH^+ .

Example 7: 4-[benzoxazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



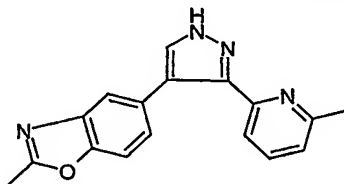
Intermediate 26 (0.45g, 1.69 mmol) and ethyl formimidate hydrochloride (0.278g, 2.5 mmol) were reacted as described for example 4, to afford, after chromatography on silicagel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9/1), the title compound as a cream oil (0.14g, 29.98%); [APCI MS] $m/z = 277$ MH^+ .

Example 8: 4-[benzoxazol-5-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



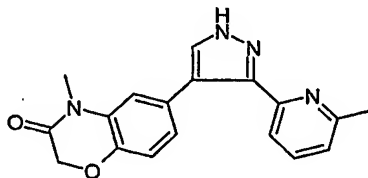
Intermediate 27 (0.25g, 0.94mmol) and ethyl formimidate hydrochloride (0.155g, 1.41mmol) were reacted as described for example 4 to afford, after crystallisation from CH₃CN/CH₂Cl₂, the title compound as yellow crystals (0.1g, 38.55%); m.p. 236-238°C; [APCI MS] m/z= 277 MH⁺.

Example 9: 4-[2-methyl-benzoxazol-5-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole



Intermediate 27 (0.25g, 0.94mmol) and ethyl acetimidate hydrochloride (0.154g, 1.41 mmol) were reacted as described for example 4 to afford, after crystallisation from CH₃CN/CH₂Cl₂, the title compound as yellow crystals (0.04g, 14.67%); m.p. 208-210°C; [APCI MS] m/z= 291 MH⁺.

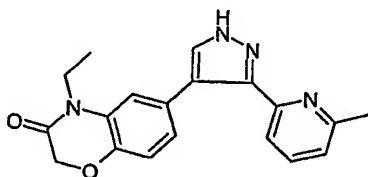
Example 10: 4-[4-methyl-4H-benzo[1,4]oxazin-3-one-6-yl]-3-(6-methylpyridin-2-yl)-1H-pyrazole



To a solution of intermediate 29 (1g, 1.8mmol) in acetone (60ml) were added cesium carbonate (0.88g, 2.7 mmol) and methyl iodide (0.17ml, 2.7 mmol) and the mixture was heated at 60°C for 4 hours and then poured into water. After extraction with CH₂Cl₂, the organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in a mixture of methanol (50ml) and 1N HCl (15ml) and the mixture was heated under reflux for 3 hours. On cooling the mixture was poured into water, neutralised with a solution of 1N NaOH and extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄ and concentrated under reduced

pressure. The residue was purified by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95/5). After trituration with pentane, the title compound was obtained as a cream solid (0.1g, 17.12%); m.p. 204-206°C; [APCI MS] m/z 321 MH^+ .

5 Example 11 : 4-[4-ethyl-4H-benzo[1,4]oxazin-3-one-6-yl]-3-(6-methylpyridin-2-yl)-1H-pyrazole



Intermediate 29 (1g, 1.8mmol) was reacted with ethyl iodide as described for example 10 to afford, after trituration with pentane, the title compound as a cream solid (0.16g, 26.25%); m.p. 182-184°C; [APCI MS] m/z 335 MH^+ .

Biology

The biological activity of the compounds of the invention may be assessed using the following assays:

15 Assay 1 (Cellular transcriptional assay)

The potential for compounds of the invention to inhibit TGF- β signalling may be demonstrated, for example, using the following *in vitro* assay.

The assay was performed in HepG2 cells stably transfected with the PAI-1 promoter (known to be a strong TGF- β responsive promoter) linked to a luciferase (firefly) reporter gene. The compounds were selected on their ability to inhibit luciferase activity in cells exposed to TGF- β . In addition, cells were transfected with a second luciferase (Renilla) gene which was not driven by a TGF- β responsive promoter and was used as a toxicity control.

96 well microplates were seeded, using a multidrop apparatus, with the stably transfected cell line at a concentration of 35000 cells per well in 200 μl of serum-containing medium. These plates were placed in a cell incubator.

18 to 24 hours later (Day 2), cell-incubation procedure was launched. Cells were incubated with TGF- β and a candidate compound at concentrations in the range 50 nM to 10 μM (final concentration of DMSO 1%). The final concentration of TGF- β (rhTGF β -1) used in the test was 1 ng/mL. Cells were incubated with a candidate compound 15-30 mins prior to the addition of TGF- β . The final volume of the test

reaction was 150 μ l. Each well contained only one candidate compound and its effect on the PAI-1 promoter was monitored.

Columns 11 and 12 were employed as controls. Column 11 contained 8 wells in which the cells were incubated in the presence of TGF- β , without a candidate compound. Column 11 was used to determine the 'reference TGF- β induced firefly luciferase value' against which values measured in the test wells (to quantify inhibitory activity) were compared. In wells A12 to D12, cells were grown in medium without TGF- β . The firefly luciferase values obtained from these positions are representative of the 'basal firefly luciferase activity'. In wells E12 to H12, cells were incubated in the presence of TGF- β and 500 μ M CPO (Cyclopentenone, Sigma), a cell toxic compound. The toxicity was revealed by decreased firefly and renilla luciferase activities (around 50 % of those obtained in column 11).

12 to 18 hours later (day 3), the luciferase quantification procedure was launched. The following reactions were performed using reagents obtained from a Dual Luciferase Assay Kit (Promega). Cells were washed and lysed with the addition of 10 μ l of passive lysis buffer (Promega). Following agitation (15 to 30 mins), luciferase activities of the plates were read in a dual-injector luminometer (BMG lumistar). For this purpose, 50 μ l of luciferase assay reagent and 50 μ l of 'Stop & Glo' buffer were injected sequentially to quantify the activities of both luciferases. Data obtained from the measurements were processed and analysed using suitable software. The mean Luciferase activity value obtained in wells A11 to H11 (Column 11, TGF- β only) was considered to represent 100% and values obtained in wells A12 to D12 (cells in medium alone) gave a basal level (0%). For each of the compounds tested, a concentration response curve was constructed from which an IC₅₀ value was determined graphically.

Assay 2 (Alk5 Fluorescence Polarization Assay)

Kinase inhibitor compounds conjugated to fluorophores, can be used as fluorescent ligands to monitor ATP competitive binding of other compounds to a given kinase.

The increase in depolarization of plane polarized light, caused by release of the bound ligand into solution, is measured as a polarization/anisotropy value. This protocol details the use of a rhodamine green-labelled ligand for assays using recombinant GST-ALK5 (residues 198-503).

Assay buffer components: 62.5 mM Hepes pH 7.5 (Sigma H-4034), 1 mM DTT (Sigma D-0632), 12.5 mM MgCl_2 (Sigma M-9272), 1.25 mM CHAPS (Sigma C-3023).

Protocol: Solid compound stocks were dissolved in 100% DMSO to a concentration of 1 mM and transferred into column 1, rows A-H of a 96-well, U bottom, polypropylene plate (Costar #3365) to make a compound plate. The compounds were serially diluted (3-fold in 100% DMSO) across the plate to column 11 to yield 11 concentrations for each test compound. Column 12 contained only DMSO. A Rapidplate™-96 was used to transfer 1 μl of sample from each well into a 96-well, black, U-bottom, non-treated plate (Costar #3792) to create an assay plate.

ALK5 was added to assay buffer containing the above components and 1 nM of the rhodamine green-labelled ligand so that the final ALK5 concentration was 10 nM based on active site titration of the enzyme. The enzyme/ligand reagent (39 μl) was added to each well of the previously prepared assay plates. A control compound (1 μl) was added to column 12, rows E-H for the low control values. The plates were read immediately on a LJL Acquest fluorescence reader (Molecular Devices, serial number AQ1048) with excitation, emission, and dichroic filters of 485nm, 530 nm, and 505 nm, respectively. The fluorescence polarization for each well was calculated by the Acquest reader and then imported into curve fitting software for construction of concentration response curves. The normalized response was determined relative to the high controls (1 μl DMSO in column 12, rows A-D) and the low controls (1 μl of control compound in column 12, rows E-H). An IC_{50} value was then calculated for each compound

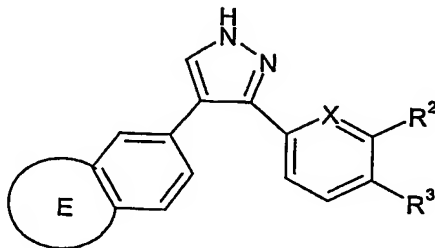
Using the above assays all Examples of the invention show ALK5 receptor modulator activity (having IC_{50} values in the range of 1 to 100nM) and TGF- β cellular activity (having IC_{50} values in the range of 0.001 to 10 μM):

4-[1-Ethyl-benzimidazol-6-yl]-3-[6-methylpyridin-2-yl]-1H-pyrazole (Example 1) showed an ALK5 receptor modulator activity of 25 nM and TGF- β cellular activity of 5 nM.

4-[4-Methyl-4H-benzo[1,4]oxazin-3-one-6-yl]-3-(6-methylpyridin-2-yl)-1H-pyrazole
(Example 10) showed an ALK5 receptor modulator activity of 32 nM and TGF- β
cellular activity of 17 nM.

Claims

1. The use of a compound of formula (I), a pharmaceutically acceptable salt, solvate or derivative thereof;



(I)

wherein

ring E is a saturated, unsaturated or aromatic 5 or 6-membered heterocycle which heterocycle in addition to carbon contains one or more ring-heteroatoms independently selected from nitrogen and oxygen, wherein the heterocycle is optionally substituted on any nitrogen atom where appropriate by one or more groups R^{Ea} independently selected from C₁₋₆alkyl and C₁₋₆alkoxyC₁₋₆alkyl and is optionally substituted on any carbon atom where appropriate by one or more groups R^{Eb} independently selected from oxo, C₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxy and halo;

X is N or CH;

R² is hydrogen, C₁₋₆alkyl, halo, cyano or perfluoroC₁₋₆alkyl; and

R³ is hydrogen or halo;

in the preparation of a medicament for treating or preventing a disease or condition mediated by ALK-5 inhibition.

2. The use according to claim 1 where the benzofused ring system including E is selected from the list: benzimidazol-6-yl, benzimidazol-5-yl, benzoxazol-6-yl, benzoxazol-5-yl, 4H-benzo[1,4]oxazin-3-one-6-yl, benzo[1,3]dioxol-5-yl, benzodioxan-6-yl, quinolin-6-yl and benzotriazol-6-yl.

3. The use according to any preceding claim where X is N.

4. The use according to any preceding claim where R² is hydrogen, C₁₋₆alkyl, chloro or fluoro.

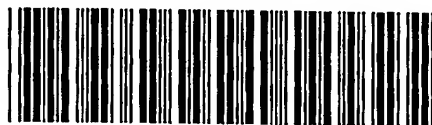
5. The use according to claim 4 where R^2 is hydrogen, methyl, chloro or fluoro.
6. The use according to claim 5 where R^2 is methyl.
7. The use according to any preceding claim where R^3 is hydrogen or halo.
8. The use according to any one of claims 1 to 3 wherein, when X is N, R^2 is methyl.
9. The use according to claim 8 wherein when X is N and R^2 is methyl, R^3 is H.
10. The use according to any preceding claim wherein the disease or condition mediated by ALK-5 inhibition is preferably selected from the list: chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers (including diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers), ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis and primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis and keloids. Preferably kidney fibrosis.

Abstract

The invention relates to novel pyrazole derivatives which are inhibitors of the transforming growth factor, ("TGF")- β signalling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF- β type I or activin-like kinase ("ALK")-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a disease state mediated by this pathway.

A80

PCT/EP2004/006427



**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.